DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

April 09, 2001

CBER-01-021

# WARNING LETTER

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

David J. Williams
President and COO
Aventis Pasteur, Inc.
Discovery Drive
Swiftwater, Pennsylvania 18370-0187

Dear Mr. Williams:

The Food and Drug Administration (FDA) conducted an inspection of Aventis Pasteur, Inc., located at Discovery Drive, Swiftwater, Pennsylvania, between January 29 and February 16, 2001. During the inspection, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and deviations from the applicable standards and requirements of Title 21, Code of Federal Regulations (CFR), Subchapter C, Parts 210 and 211, and Subchapter F, Parts 600-680, as follows:

1. Failure to conduct and document a thorough investigation of an unexplained discrepancy or the failure of a batch or any of its components to meet its specifications or extend the investigation to other batches that may have been associated with the specific failure or discrepancy [21 CFR 211.192] in that out-of-specification (OOS) results for residual moisture for various stability lots of Yellow Fever single dose units were not investigated. Examples include lots UA071AA, UA088AA, and 7275.

2. Failure to maintain and follow an appropriate written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)]. Examples include:

   a) There were no data available to demonstrate the sterility of some of the diluents supplied with vaccine products at the end of shelf life.

   b) There are no written procedures for the collection and disposition of stability samples.

3. Failure to establish, maintain, and follow written procedures for production and process control designed to assure that the drug products have the identify, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

   a) Tripedia lot U0356B did not meet specifications for visual inspection. The lot was not rejected as required by procedure J000181, "Instructions For The Sampling And Visual Inspection of Filled Product."

   b) There are no limits established for the total number of rejects allowed per filling operation.

   c) The Standard Work Instruction J000036, "Inspection Procedures for Syringes, Lyophilized Vials and Liquid Prefilled Vials," rejected vial category of "other" is too broadly defined for adequate visual inspection documentation.

   d) The current particulate rejection action limit of [redacted] for Yellow Fever is not based on historical data.

4. Failure to establish procedures to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that the manufacturing processes for Diphtheria and Tetanus Toxoids have not been validated.

5. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.165(e)]. For example:

   a) Numerous assays used in release testing of final products and testing of intermediates have not been validated.

   b) Evaluation of the Bacteriostatic and Fungistatic (B&F) properties of Yellow Fever vaccine, Mumps Skin Test Antigen (MSTA), Tetanus Toxoid Adsorbed USP and Tetanus Toxoid USP have not been completed.

   c) The use of [redacted] for residual moisture release testing of single dose Yellow Fever vaccine has not been validated.

6. Failure to establish appropriate time limits for the completion of each phase of production of Influenza Virus Vaccine to assure quality of the drug product [21 CFR 211.111]. For example:

   a) The maximum hold time for the concentrated fluids prior to [redacted] have not been validated.

b) The hold time for the pooled fractions collected after [redacted] have not been validated.

c) The hold time for the [redacted] bulk prior to [redacted] have not been established.

d) The maximum hold time for the sterilized finished concentrate have not been established.

7. Failure to assure an adequate system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)] in that there is no environmental air monitoring during the loading and unloading of the lyophilizer and during the [redacted] of the sterile bulk to the filling line.

8. Failure to establish and follow written procedures for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)] in that the [redacted] units used in the manufacture of Influenza Virus Vaccine and Tetanus Toxoid have no cleaning validation or established maximum number of uses.

9. Failure to notify the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (CBER), of errors and accidents in the manufacture of products that may affect the safety, purity, or potency of any product [21 CFR 600.14(a)]. Examples include:

a) Yellow fever single dose unit lot UA071AA did not meet specifications for [redacted] and [redacted] at the 12-month stability time point.

b) Yellow fever single dose unit lot UA088AA did not meet specifications for [redacted] at the 6-month time point.

c) Yellow fever single dose unit lot 7275 did not meet specifications for [redacted] at the 6 and 12-month stability time points.

d) Yellow fever twenty-dose unit lot U7042/0975910 did not meet specifications for [redacted] at the 6 and 12-month time points.

We acknowledge receipt of your March 16, 2001, written response, which addresses the inspectional observations on the Form FDA 483, issued at the close of the inspection. We will address your response under separate cover.

Neither the above violations nor the observations noted on the Form FDA 483, presented at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations

noted in this letter and on the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing process. You are responsible for investigating and determining the causes of the violations identified by the FDA.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure, injunction, and/or civil penalties. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplement for drugs to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to the FDA in writing within 15 working days of receipt of this letter of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. Corrective actions addressed in your March 16, 2001 submission may be referenced in your response to this letter, as appropriate. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of the promised corrective actions during the next inspection of your facility.

Your written reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

Mary A. Malarkey
for

Deborah D. Ralston
Director
Office of Regional Operations